Online ISSN : 2249-4618
Print ISSN : 0975-5888
DOI : 10.17406/GJMRA

Global Journal

of Medical Research: C

Microbiology and Pathology



Surface Squamous Neoplasia

Uveitis Patients at a Tertiry

Highlights

Molecular Typing of HLA B27

Issues of Clinical Immunology

Discovering Thoughts, Inventing Future

VOLUME 19 ISSUE 2 VERSION 1.0

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Volume 19 Issue 33 was originally issued as C2

Global Journal of Medical Research: C
Microbiology and Pathology

Volume 19 Issue 33
Originally issued as C2



Global Journal of Medical Research: C
Microbiology and Pathology

Volume 19 Issue 2 (Ver. 1.0)

Open Association of Research Society

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USA Toll Free: +001-888-839-7392
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Offset Typesetting

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Global Journal of Medical Research: C
Microbiology and Pathology
Volume 19 Issue 2 Version 1.0 Year 2019
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Controversial Issues of Clinical Immunology. Modern Concepts about the Pathogenesis of Infections

By Zemskov, V. M., Zemskov, A. M., Pronko, K. N., Afanasiev, S. S., Zemskova, V. A. & Revishvili, A. Sh.

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Abstract- It is postulated that a suppressed or stimulated state of immune reactivity plays an important role in the induction of an infection process, which triggers the activation of microbiota pathogens. Infection-driven destruction of cells of a macroorganism promotes the release of endogenous low molecular weight nucleic acids, mostly RNA, which, within the first hours/days, are responsible for the stimulation of replication and toxin formation by microflora with subsequent disease exacerbation, and as a result, in a few days, cause an increase in antigenicity, immunogenicity, antibiotic susceptibility of pathogens, and activation of nonspecific and specific resistance of the body, with the resulting immune activation. Concurrently with these processes, the intensification of free-radical lipid and protein oxidation is observed, with the formation of immunosuppressive compounds which are neutralized by enzymatic and nonenzymatic factors of the antioxidant system. Thus, in infection processes homeostasis is achieved by means of a sequential cascade of microbial, immune, and metabolic mechanisms which induce, stimulate, and inhibit the responsiveness of the body.

Keywords: microbiota, hospital-acquired infection, antioxidants, metabolic processes, low molecular weight RNA.

GJMR-C Classification: NLMC Code: QW 180



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Controversial Issues of Clinical Immunology. Modern Concepts about the Pathogenesis of Infections

Zemskov, V. M. [α], Zemskov, A. M. [σ], Pronko, K. N. [ρ], Afanasiev, S. S. [ω], Zemskova, V. A. [¥] & Revishvili, A. Sh. [§]

Abstract- It is postulated that a suppressed or stimulated state of immune reactivity plays an important role in the induction of an infection process, which triggers the activation of microbiota pathogens. Infection-driven destruction of cells of a macroorganism promotes the release of endogenous low molecular weight nucleic acids, mostly RNA, which, within the first hours/days, are responsible for the stimulation of replication and toxin formation by microflora with subsequent disease exacerbation, and as a result, in a few days, cause an increase in antigenicity, immunogenicity, antibiotic susceptibility of pathogens, and activation of nonspecific and specific resistance of the body, with the resulting immune activation. Concurrently with these processes, the intensification of free-radical lipid and protein oxidation is observed, with the formation of immunosuppressive compounds which are neutralized by enzymatic and nonenzymatic factors of the antioxidant system. Thus, in infection processes homeostasis is achieved by means of a sequential cascade of microbial, immune, and metabolic mechanisms which induce, stimulate, and inhibit the responsiveness of the body.

Keywords: microbiota, hospital-acquired infection, antioxidants, metabolic processes, low molecular weight RNA.

I. Introduction

The modern trend for increase in infectious morbidity, with modifications of the characteristic features of infections, including immune ones, is indicative of a distortion of population resistance and low efficacy of diagnostic and treatment techniques (Vorobyev et al., 2010; Pokrovsky et al., 2013; Zemskov AM and Zemskov VM, 2016; Pokrovsky, 2012).

A concept of the "main components of the pathogenesis of infections," i.e. immune reactivity—microbiota—nucleic acids—metabolic processes, has been developed based on the analysis of modern data.

a) *Interactions between Immune Reactivity and Microbiota during Infection Processes*

i. *Immune Reactivity*

Immune reactivity is determined by the number and activity of lymphoid phagocytic cells observed in circulating blood and locally in tissues, the state of the complement system, nonspecific resistance parameters, killer cells, immune globulins, specific antibodies, cytokines, and other parameters in a given patient at the present moment (Zemskov et al., 2016a).

ii. *Colonization Resistance*

Immune reactivity is contiguous with the phenomenon of colonization resistance of mucosa of exposed body cavities, i.e. resident microflora, the composition of which is determined by microbial adhesion inhibitors, biocidal and biostatic secretory products, mechanical factors (ciliated epithelium, integrity of the skin and mucosa, mucociliary epithelium movement, bowel motility, mucosal cell desquamation), antimicrobial effects of salivary secretion, bile, gastrointestinal contents, the composition and the amount of mucin, oxygen tension through the thickness of biofilm, pH of the medium, and by environmental factors (Karaulov et al., 2017).

iii. *Microbiota (microbiocenosis)*

It includes bacteria, spirochetes, bacteriophages, mycoplasma, chlamydia, rickettsia, viruses, prions, and other microorganisms on the surface of the skin and mucosa of exposed cavities. Diseases of microbiota (dysbiosis) are disturbances of the balance between representatives of normal microflora of the body characterized by significant abnormal quantitative and qualitative composition of microbiocenosis. According to recent data, anaerobes account for 90% of normal intestinal microflora, thus they cannot grow on conventional media. In other words, what is known as dysbiosis accounts for 10% of the existing reality (Zemskov et al., 2016a).

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There are 4 stages of dysbiosis: normocenosis (I), intermediate (II), dysbiosis (III), and significant inflammation (IV). It is generally assumed that stage I or II dysbiosis is observed in healthy patients, and stage III or IV dysbiosis—in patients with premonitory symptom and favorable course of the infection. In case of recovery and eradication of the pathogen, a reversion to stage I or II takes place, while in cases of chronic diseases stage III or IV dysbiosis is observed for a longer period of time (Karaulov et al., 2017).

There are several possible associations between the immune reactivity level in patients and their microbiota.

1. In healthy individuals, there is a balance between microbiota mostly represented by commensals (despite the lack of clear delineation between them and opportunistic pathogens) and immune reactivity.
2. In immune compromised patients (AIDS), slightly virulent and even saprophytic microflora of the skin and mucosa may become capable of causing infectious disorders.
3. In case of immune reactivity activation due to the accumulation of antibacterial factors, such as lysozyme, lactoferrin, stimulated neutrophils, macrophages, immune globulins, etc., in the epithelium, microorganisms respond with the activation of aggression enzymes, such as neuraminidase and hyaluronidase, release of endotoxins, etc., with a certain probability of promoting infections.
4. In some cases, pathological conditions due to highly virulent pathogens develop irrespective of a patient's immune status and microbiocenosis.
5. These processes are controlled by built-in pattern recognition receptors (PRRs), which are conservative molecular structures only found in microorganisms (pathogen associated molecular patterns (PAMPs)) and which control cytokine cascade, inflammatory reactions, immunoglobulin production, etc. There are several PRR families: TOLL-like receptors, NOD-like receptors, mannose lectin and scavenger receptors, and complement system factor receptors. For example, the activation of mucosal TOLL-like receptors (TLR-4) regulates resistance against gram-negative pathogens, TLR-2—against gram-positive pathogens, and TLR-3 and TLR-8—against viral pathogens (Karaulov et al., 2017).

b) The Role of Nucleic Acids in Immune Response, Infections, and Metabolic Processes

Development of any pathological processes and a number of physiological ones is accompanied by destruction of cells of various tissues of the body caused by microorganisms, their toxins, aggression enzymes, etc., which results in enrichment of the internal environment with fragments of low molecular weight nucleic acids and factors promoting their release. This is confirmed by published data, according to which significant changes in plasma concentrations of nucleic acids, primarily RNAs, are observed during various infectious diseases. They include the following: nonspecific pulmonary inflammatory diseases, acute dysentery, viral hepatitis, pyelonephritis, purulent processes, etc. (Zemskov et al., 2016b).

i. *Effect on Immune Reactivity*

In model experiments during the administration of low molecular weight RNA in rodents 4–24 hours before inoculation, stimulation of nonspecific protection factors, such as the complement and properdin systems, interferons, β-lysines, and infectious agent growth inhibitors is observed, together with promotion of mobility, as well as absorbing and metabolic capacity of monocytes/macrophages. At later stages, they are accompanied by the stimulation of specific cell-mediated and antibody-mediated immune response. The spectrum of action of ribonucleotides includes quantitative and functional characteristics of the main populations and subpopulations of lymphoid cells, phagocytic activity, processes of stem cell differentiation, cooperation of T- and B-lymphocytes and macrophages, formation of cytokines, desensitization of the body, immune memory depression, antigen redeposition, expression of various cell receptors, etc. These dynamic processes are differently directed and implement the intimate mechanism of immune system homeostasis regulation.

The following biological phenomena were observed in model experiments and clinical observations when using sodium nucleinate (sodium salt of low molecular weight yeast RNA), an equivalent of ribonucleotides naturally released during infection processes (Zemskov et al., 2013).

a. *Antiviral Action*

Antiviral action is mediated by activation of T- and B-cell dependent immune responses, phagocytosis, interferon formation, and other mechanisms.

b. *Detoxication*

Detoxication is ensured by the normalization of nucleic-protein synthesis, stimulation of phagocytosis, reparative processes in the liver, an increase in the activity of several enzymes, etc.

c. *Adjuvanticity*

Adjuvanticity is implemented through potentiation of cell-mediated and antibody-mediated immune responses, phagocytic component, activation of stem cell and T-helper migration, cooperation of main cell participants of immune response, RNA and antigen complex formation which leads to a rapid increase in immunogenicity of the antigen. This also boosts the

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primary and secondary immune responses to thymus-dependent and thymus-independent antigens, corpuscular, chemical, mixed, and live vaccines, as well as anatoxins.

d. *Revaccination Effect*

The revaccination effect is induced as a result of increased interaction between T- and B-cells with macrophages, antigen redeposition, and immune memory cell depression.

e. *Immune Modulation*

It is based on the pluripotent effect of low molecular weight RNA on metabolic and immune processes.

f. *Desensitization*

Desensitization is mediated by modulation of the suppressor component of the immune system, stabilization of membranes and enzyme systems of the respective cells destroying biogenic amines, etc.

c) *The Mechanism of Implementation of General Biological Effects of Nucleic Acids*

As for the mechanism of implementation of general biological effects of RNA, they are still understudied. According to published data, nucleic acids and, first of all, RNA replenish the supply of substances required for metabolism, thus affecting vital functions of the body in general. Ribonucleotides and their components form a part of many cell metabolism products (ATP, GTP, UTP, CMP), as well as several coenzymes and phospholipids required for normal performance of certain functions. It is noteworthy that ATP is an energy source, cytosine nucleotides are involved in the synthesis of lipids, uridine—in polysaccharide metabolism, and guanine nucleotides—in the synthesis of proteins. Apparently, this mechanism is not the only one or the main one. In any case, W. Braun states the following in the context of microorganisms: "... actual stimulation of cell multiplication turns out to be significantly greater than estimated stimulation based on the assumption that endogenous nucleic acids are only used as building blocks" (Braun, 1968). It is certain that an indirect path of action of nucleic acids on cells exists, probably through a system of cyclic nucleotides. Their effect through the respective nucleotide receptors on the cellular membrane also cannot be ruled out as it was suggested that some receptors for fragments of low molecular weight RNA exist on cell surface and translate its effect. It has been shown that in cases of the effect of healthy individuals' lymphocytes on receptors, purine nucleotides demonstrate a stimulating effect to a greater extent, while pyrimidine nucleotides are mostly characterized by inhibitory effects. AMP demonstrates the highest activity, while GMP has the lowest activity, and a combination of complementary GMP and CMP was highly productive. However, it turned out to be less active than the total "natural" product sodium nucleinate and a complex of four nucleotides. Inhibition of the expression of specific receptors in immature pre-B-cells and their stimulation in pre-T-cells is observed. Minimum changes have been observed for lymphocytes with helper and suppressor functions. At the same time, in patients with acute dysentery, the expression of cell receptors was inhibited to the greatest extent due to the effect of AMP purine, CMP pyrimidine, and a combination of both. All mononucleotides and their combinations had minimum impact on T-suppressors, while GMP+CMP promoted their inhibition. GMP+UMP ensured significant stimulation of the expression of B-cell receptors. There are still no data on the effect of these changes in the receptor apparatus on the properties of lymphocytes, but various biological effects of mononucleotides have been confirmed. CMP and UMP 9–19-fold stimulate antibody-producing cells formation, while AMP decreases their formation 10-fold against the baseline. On the other hand, AMP inhibits antigen-specific reactions and increases delayed hypersensitivity (Zemskov et al., 2016b).

d) *Effect on Infection*

Accumulation of low molecular weight ribonucleotides in the body stimulates the growth of microorganisms of various taxonomic groups, selection of their virulent clones, and production of exotoxins early in the course of an infection process, which is accompanied by infection potentiation. This phenomenon was documented in model experiments with administration of a broad spectrum of gram-positive, gram-negative, and other pathogens in susceptible animals along with RNA preparations. This caused an obvious worsening of the infection, which was judged based on the decrease in LD_{50} values, survival rate, and average life span of rodents, and an increase in skin necrosis area in case of an intracutaneous coinjection of gaseous gangrene pathogen and RNA preparations. Subsequently, the same nucleic acid preparation caused an increase in antigenicity, immunogenicity, specific immune defense factors, which was experimentally reproduced by administration of a nucleic acid stimulator and antigens or vaccine simultaneously or 24–72 h after the injection immune preparations of laboratory animals. When growth of microorganisms on the solid bacteriological medium was with RNA in vitro – microorganisms received antibiotic susceptibility.

e) *Effect on the Metabolic Processes of the Macroorganisms*

The following effects were documented when using low molecular weight RNA in vitro experiments, in vivo experiments, and clinical observations (Zemskolv et al., 1985a; Zemskov V. M. and Zemskov A.M., 1992).The stimulation of RNAs, DNAs, and protein synthesis, the accumulation of ATP and ADP, and the activation

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of monoaminooxidase and α-glycerophosphate dehydrogenase was observed in lymphocytes of the spleen; the increased biosynthesis of mitochondrial, nuclear, and cytoplasmic RNAs and the increased activity of tryptophan pyrrolase were observed in the liver. Increased oxygen consumption and decreased glycolysis rate were observed in normal granulocytes. The activation of protein formation was observed in bone marrow and brain cells and in tumor cell cultures, while macrophages were characterized by the activation of glycolysis, oxidative phosphorylation, amino acid catabolism, increased activity of dehydrogenases, mitochondrial α-glycerophosphate dehydrogenase, glutamate dehydrogenase, β-oxybutyrate dehydrogenase, nonspecific esterase, the increased amount of protein and glycogen, the expression of Fc*γ* receptors, and oxygen metabolism (Shcherbakova et al., 1981; Zemskov et al., 1985b; Zemskov V. M. and Zemskov A. M., 1992). An early activation of lactate dehydrogenase responsible for intensification of glycolytic processes, malate dehydrogenase which serves as an energy supply marker, and glutamate dehydrogenase which reflects the intensity of amino acid metabolism was observed in thymus cells under the action of yeast RNA. The spectrum of targets of these biologically active compounds includes formation and interaction of cyclic nucleotides cAMP/cGMP which are known to regulate mitotic processes in various cells which act as second messengers that mediate the effects of corticosteroids, other hormones, enzyme systems of various cells, etc.

f) Free-radical Lipid and Protein Oxidation and the Antioxidant System as Bio regulators

i. *Free-radical Oxidation Processes*

These processes are central to cell metabolism. They act as a source of energy required for vital functions of a cell and the organism as a whole, "prepare" organic substances for cell structures, and participate in the metabolism of carbohydrates, lipids, proteins, and nucleic acids. Reactions of mitochondrial and microsomal oxidation resulting from incomplete reduction of oxygen to water produce active forms, such as singlet oxygen, superoxide anion radical, hydroxyl radical, hydroperoxyl radical, and hydrogen peroxide, which form peroxide compounds in the presence of mixed-valent metal ions.

The high biological activity of free-radical oxidation products determines two opposite types of their action in the body. The primary products which are normally observed in relatively low concentrations have a positive effect, i.e. reversible transformations of fatty acid residues of membrane phospholipids of various cells, with a positive change in the functional state of biomembranes and their enzymes. The secondary products of free-radical oxidation have a damaging effect on the structural and functional state of biomembranes, biomolecules and, first of all, proteins, including those of the immune system. Diene conjugates, ketodiens, malondialdehyde, fluorescent Schiff bases, CO-terminal residues of amino acids, bityrosine cross-links, etc., act as free-radical oxidation markers (Luzkiy et al., 2016).

ii. *Antioxidant Defense System*

Accumulation of toxic immunosuppressive molecules in the body requires the presence of a balanced antioxidant defense system consisting of enzymatic (superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, ceruloplasmin) and nonenzymatic (peroxidase resistance of red blood cells, α-tocopherol, antiradical activity of lipids, total, nonprotein and protein thiols, total antioxidative activity) mechanisms. The balanced interaction of enzymatic and nonenzymatic components of an endogenous antioxidant defense system ensures stable free-radical chain reactions and the maintenance of concentrations of reactive oxygen species, free radicals, and molecular products of free-radical lipid and protein oxidation at a stationary level.

Free-radical lipid and protein oxidation reactions that are not balanced by the antioxidant defense result in oxidative stress in immune cells, which has a negative impact on the membranes and receptors of immune competent cells, which interferes with the cooperation processes, immune response development, and other phenomena, including those observed during infection processes (Zemskov et al., 2016b).

g) Correlations between Immune-metabolic Parameters

The presence of mathematically significant associations confirms involvement of the components discussed above in the pathogenesis of infections. It has been established that parameters of immune-laboratory status form a matrix of integrative associations of some kind, including intrasystem (between immune parameters), intersystem (between immune and routine hematological parameters), and non-system (between immune and metabolic parameters) associations.

i. *Intra- and Intersystem Associations between Immune-metabolic Parameters*

a. *Healthy Individuals*

In healthy individuals, T-cells were mathematically positively associated with total lymphocytes and monocytes, T-helpers—with total T-cells, lymphocytes, and monocytes, and B-cells had the same set of correlations with T-cells, T-helpers, cytotoxic T lymphocytes, and monocytes. Total T-cells, T-helpers, and B-cells had a positive correlation with segmented cells, and the phagocytic number had a negative correlation with stab cells. Total T-cells had a negative correlation with basophiles, and T-helpers—with eosinophils, while the phagocytic number had a positive correlation with the same cells.

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b. *Purulent Soft Tissue Infection*

In this pathology, there was a positive correlation between cytotoxic T lymphocytes and white blood cells, a negative correlation between eosinophils and lymphocytes, and a positive correlation between B-cells and IgG and T-helpers.

c. *Acute Adnexitis*

In cases of acute adnexitis, IgM, IgA, and circulating immune complexes were characterized by a positive correlation with the white blood cell count, lymphocyte count, the level of proinflammatory TNF-α, and had a negative correlation with the level of natural killer cells, T-helpers, IgG, and phagocytic index. In patients with urogenital chlamydiosis, IgM, oxygen activity of phagocytes determined by nitrobluetetrazolium reduction and total T-cells formed positive correlations with B-cells, T-helpers, phagocytes, lymphocytes, and natural killer cells.

d. *HbsAg Carriers*

In HbsAg carriers, lymphocytes and stab cells had a positive correlation with T-cells and IgM, while segmented cells and eosinophils had a negative correlation with T-cells and IgG, and T-cells were characterized by a positive correlation with null cells. There was a positive correlation between the monocyte count and the level of T-helpers, cytotoxic T lymphocytes, and the phagocytic number (Zemskov et al., 2007).

ii. *Non-system Associations between Immune-metabolic Parameters*

a. *Healthy Individuals*

In healthy individuals, the level of total T-cells had positive correlations with the «thymol test», blood amylase, cholesterol, prothrombin, antioxidative activity of plasma, and superoxide dismutase activity, and a negative correlation with alanine aminotransferase. Cytotoxic T lymphocytes had a correlation with total and indirect bilirubin, «thymol test», blood amylase, glucose, and alanine aminotransferase. T-helpers had a mathematical association with the «thymol test», prothrombin, and the antioxidative activity of plasma and superoxide dismutase. All three types of cells were characterized by a reliable negative correlation with alanine aminotransferase. Killer lymphocytes were dependent on the antioxidative activity of plasma and superoxide dismutase. The levels of total and direct bilirubin, prothrombin, the antioxidative activity of plasma and superoxide dismutase had a positive correlation with the B-cell count.

b. *Serous Meningitis*

In children with serous meningitis, there was a positive correlation between T-cells and their regulatory subpopulations, phagocytic index and alanine aminotransferase, B-cells and albumin, as well as phagocytic number and α-1 and β-protein fractions.

c. *Purulent Meningitis*

In cases of a more severe purulent meningitis, cytotoxic T lymphocytes had a positive correlation with cholesterol and β-lipoproteins, while T- and B-cells and IgM had a positive correlation with blood protein fractions.

d. *Nonspecific Pulmonary Inflammatory Diseases*

Nonspecific pulmonary inflammatory diseases in adults are characterized by inverse relationship between the level of ribonucleotides and the null cell count, and direct relationship with T-cells and IgA. T-cells, cytotoxic T lymphocytes, and T-helpers had a negative correlation with lipid peroxidation products, i.e. malondialdehyde and glutathione peroxidase, circulating immune complexes and average weight molecules. Thus, the studies have shown that infectious diseases of the bronchopulmonary system are accompanied by an activation of lipid peroxidation processes, which results in an increase of cholesterol and β-lipoprotein level, along with a decrease in antioxidant defense activity, accumulation of biogenic amines, an increase in the level of polyunsaturated fatty acids in the bronchoalveolar contents, and a decrease in the content of more saturated acids. These changes are observed against the development of disnucleotidosis in patients, i.e. a violation of protein synthesis processes implemented according to the "DNA→RNA→protein" scheme. On the one hand, it causes inhibition of immune responses, especially cell-mediated ones, and imbalance of regulatory lymphoid cell subpopulations; on the other hand, it promotes the development of allergic reaction; on the third hand, it results in the functional and destructive changes in cells of the bronchopulmonary system and other systems of the body; and on the fourth hand, it causes disorders which are closely associated with immune and neuroendocrine homeostasis regulation (Zemskov et al., 2016c).

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Global Journal of Medical Research: C
Microbiology and Pathology
Volume 19 Issue 2 Version 1.0 Year 2019
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Molecular Typing of HLA B27 in Uveitis Patients at a Tertiry Care Centre in India and its Clinical Implications

By Indu Yadav & Indrani Dhawan

Abstract- Uveitis is a common ocular disease characterized by inflammation of iris, choroid, and ciliary body. HLA-B27 is the strongest known genetic risk factor for acute anterior uveitis. The prevalence of HLA B27 and associated diseases varies widely across different racial groups and have massive clinical implications. DNA typing was done using amplification of genomic DNA by the polymerase chain reaction (PCR) and hybridization with sequence-specific oligonucleotide probes (SSOP). This study was undertaken due to paucity of recent reports on Asian Indian population with uveitis as a predominant clinical feature.

GJMR-C Classification: NLMC Code: QZ 4



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I. Material and Methods

A total of 30 patients of uveitis and 30 healthy controls in blood bank were included in this study of two years from July 2016 to June 2018 in Department of Pathology and Department of Ophthalmology, VMMC AND Safdarjung Hospital, New Delhi. HLA B27 genotyping was performed using PCR-SSP (Fluogene -a fluorescence based HLA gene amplification detection system). It was a tertiary care center based cross-sectional study, and comparison between groups was done using Pearson's Chi-square test/ Fischer's exact test. Ap value≤ 0.05 was considered statistically significant. Patient with any malignancy and treated with radiotherapy or chemotherapy before enrolment in study were excluded. Data were entered in Microsoft excel sheet and Analysis was done on licensed version 21 of SPSS.

II. Results and Discussion

A total of 30 cases of uveitis attending Ophthalmology O.P.D at Safdarjung Hospital and 30 healthy controls from blood bank of Safdarjung Hospital were evaluated in this study by HLA B27 typing done using PCR-SSP method on all the cases and controls.

The age of the cases ranged from 15 to 80 years with a mean age of 35.7±14.08 years. Age of controls ranged from 22 to 46 years with a mean age of 31.43±7.88 years. On comparison of the incidence of HLA B27 positivity between cases and controls, out of 30 cases of uveitis 46.6% (n=14) were positive, and 53.4% (n=16) were negative. In the healthy control group 96.7% (n=29) were negative, and only one 3.3% (n=1) was positive. Chi-square analysis suggests that the cases had a significantly higher incidence of HLA B27 positivity as compared to controls. The study conducted by M. N. Mishra in Asian Indian population concluded that HLA B27 positivity rate was 56.2% among uveitis patients and 3% for control samples.[1] A study conducted in Finland showed HLA B27 positivity rate was 70% in cases of uveitis.[2] Our results were in agreement with the results of these studies. The lower positivity rate than the Finland study is probably explained by the higher frequency of HLA B27 in Caucasians.

Table I: Comparison of incidences of HLA-B27 positivity between two groups

		HLA B27		Total
		Negative	Positive	
Group	Case	16	14	30
	Control	29	1	30
		45	15	60

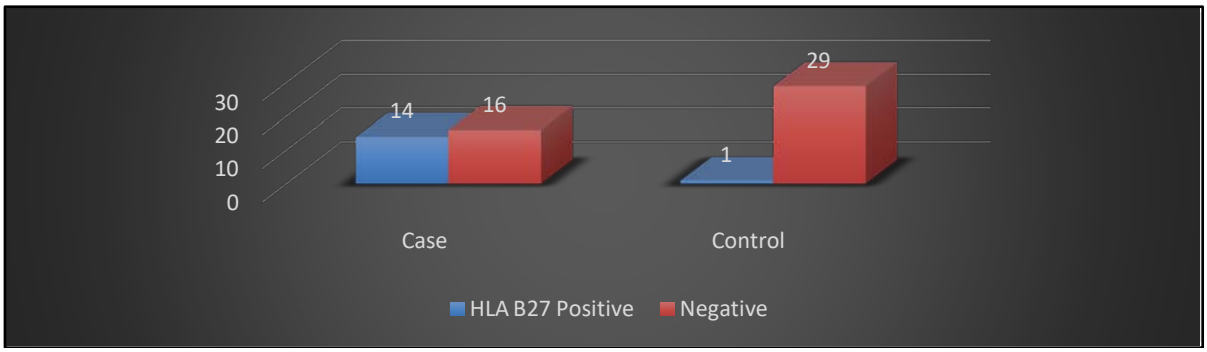


Figure 1: Comparison of incidences of HLA-B27 positivity between two groups.

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In our study out of the 14 HLA B 27 positive cases (n= 8) were in the age group of 20-41 years. In the study by Mishra et al[1], most of the patients were in the age group of 41-50 years. A study conducted by Pathanapitoon K[3] also hypothesized that the HLA B27 associated acute AU represents a distinct clinical entity occurring typically in young adults between the ages of 20 and 40 years, which similar to our study. The possible explanation is that autoimmune diseases present more in the young population.[4] Due to younger age, there is less stimulation of peripheral T regulatory cells hence protective regulatory mechanism is not enhanced.[5]

The mean age at the time of the first attack for HLA-B27 positive cases was 29.50 ± 8.3 years, whereas it was 34.56 ± 15.1 years in case of HLA B27 negative cases. This shows that HLA B27 positive cases have an early age at time of first attack of uveitis. Study by Monnet et al[6] and other authors[7] showed 31 years as mean age at the time of the first attack. Barkenburg[8] showed that there was no difference between male and female in terms of average age of onset of uveitis

Out of 30 cases of uveitis, 66.6% (n=20) were males and 33.3% (n=10) were females. Out of the 20 (66.6%) males clinically diagnosed as uveitis, 39.9% (n=12) were positive for HLA B27, whereas 26.6% (n=8) were negative for HLA B27. Of 10 (33.3%) females clinically diagnosed as uveitis, 6.6% (n=2) were positive and 26.7% (n=8) were negative for HLA B27. Chi-square test suggests that HLA B27 positivity is more frequent in male compared to females presenting of uveitis. In our study there was male preponderance which is similar to studies done by different authors across the world with a male:female ratio varying from 3:1 to 1.5:1. [1,7,9,10] Since HLA B27 molecules are major histocompatibility complex class I gene products which interact with T cells, in particular, CD8+ T cells, it is conceivable that gender-related differences in immune response could play a role in the different manifestations of HLA B27 associated uveitis. Variable environmental exposures, either endogenous (i.e., sex hormone) or exogenous (tendency towards exposure to infectious agents through lifestyle or different susceptibilities), might be expected to play roles as well.[11]

Table II: Gender preponderance in HLA B27 cases

		HLA B27		Total
		Negative	Positive	
Sex	F	8	2	10
	M	8	12	20
Total		16	14	30

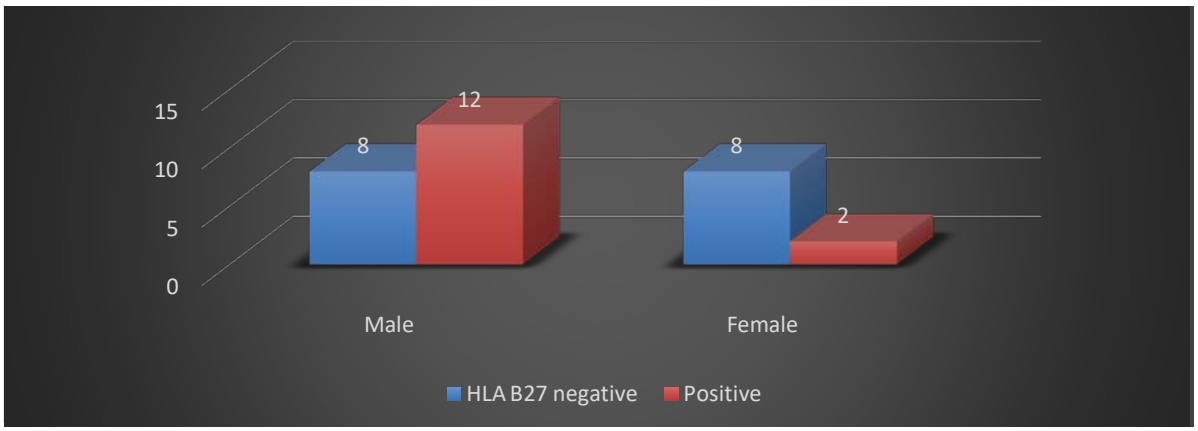


Figure 2: Gender preponderance in HLA B27 case

Our study showed that the most common systemic disease in HLA B27 positive cases is ankylosing spondylitis which constitute 21% of the HLA B27 positive cases of uveitis. Mishra found only 4.5% of uveitis patients had associated systemic disease. The study by Monnet[6] (n=175) showed that HLA B27-associated extraocular disorder was seen in 77.7% and of these, ankylosing spondylitis was diagnosed in 46.3. Similarly, in the study conducted by linseen[12] (n=119), rheumatologic complications occurred in 72% of HLA B27-positive males. So, the most common of the extraocular diseases are spondyloarthropathies. Uveitis is frequently the first indication of a previously undiagnosed HLA B27-associated extraocular disease.[12] The frequency of systemic disease associated with HLA B27 associated uveitis seems to be lower in Japan (1.3%), India (15%), and Thailand (15%) when compared with Western countries (~50%).[3]

Among uveitis cases, a number of episodes was variable ranging from 1 to 12 in all cases included in the study. The HLA B27 tested positive cases for HLA B27 showed 4.36±3.41 mean number of episodes, but the HLA B27 tested negative cases has mean 1.81 ± .911 number of episodes. Our study showed that due to more number of recurrent attack, the HLA B27 positive uveitis are more prone for the development of complication like glaucoma and cystoid macular edema. Denis Wakefield suggested that complication in HLA B27 AU patients are related to the number of recurrent attacks.[13] The patients who were HLA B27 positive,

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either with or without systemic disease, experienced a greater number of complications than did the patients who were HLA B27 negative.[14]Thus the prognosis of anterior uveitis associated with the HLA B27, either with or without associated systemic disease, is less favorable when compared with that of HLA B27-negative patients with idiopathic anterior uveitis.

Table III: Comparison of the number of episodes between HLA B27 positive and negative cases

	HLA B27	N	Mean	Std. Deviation	Std. Error Mean	p-value
No. of episodes	Negative	16	1.81	.911	.228	0.008**
	Positive	14	4.36	3.411	.912	

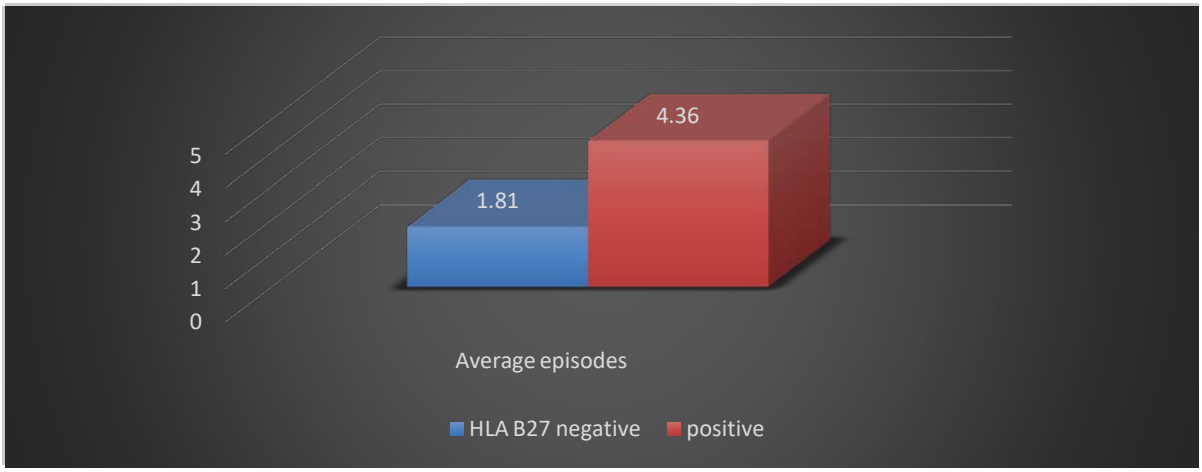


Figure 3: Comparison of the number of episodes between HLA B27 positive and negative cases

Similarly, study conducted in Asian Indian population and at other places [1,15] hypothesized that HLA B27 positive patients have a poorer prognosis than HLA B27 negative patients. On the other hand, contradictory studies are also found in the literature. This can be due to referral bias in a tertiary care centre and small sample size. The prognosis of HLA B27 associated uveitis was rather favorable or similar despite more severe inflammation and a higher recurrence rate[3,8] in these studies.

III. Conclusion

HLA B27 is frequently detected in Indian population. The joint efforts of an ophthalmologist, a rheumatologist and other specialists, can play a positive effect in treating the patients with HLA B27-associated uveitis.[16]Hence, it can be stated that HLA B27 typing in patients with AAU helps the clinician with the prognosis by avoidance of recurrent attacks and complications. This study was undertaken due to paucity of recent reports on Asian Indian population with uveitis as a predominant clinical feature. The sample size of our study was small. We recommend further multicentric studies with the large sample size for establishment of typing in uveitis and its importance in prognosis.

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Global Journal of Medical Research: C
Microbiology and Pathology
Volume 19 Issue 2 Version 1.0 Year 2019
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Hemoglobin EE Disease: A Case Report

By Awad M. Al-Qahtani, Mohamed S. M. Khalil & Essam M. Ahmed

Najran University

Abstract- *Background:* Hemoglobin E variant results from a G→A substitution resulting consequently in abnormal processing for messenger mRNA. Its interactions with various forms of α and β thalassemia produce a very wide range of clinical syndromes.

Methods: A Consent has been taken from a 26-year-old male. CBC, Glucose, Vitamin B_{12}, C-peptide, estradiol (E_2), follicle stimulating hormone (FSH), free triiodothyronine (FT_3), free thyroxine (FT_4), luteinizing hormone (LH), prolactin, parathyroid hormone (PTH), testosterone, thyroid stimulating hormone (TSH) and vitamin D_3 (25-OH) and HPLC for hemoglobin separation were performed.

Results: There was a history of hemolytic anemia due to infection with malaria and just one blood transfusion. There were no significant clinical findings such as organomegaly, icterus, or thalassemic bone changes. C-peptide, E_2 and TSH results were slightly above the normal range. Vit D was slightly insufficient. No Helicobacter pylori Antigen is stool and no clinical abnormalties. All the Hb were abnormal. The patient has low HDL-C which could not be explained. Also the slightly increased hormones of E2 and TSH, the slightly increased C-peptide could not be explained and this requires further investigations.

Conclusion: The case was reported as abnormal hemoglobin (Hb E) masking the Hb A2 on HPLC.

GJMR-C Classification: *NLMC Code: WH 190*



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Conclusion: The case was reported as abnormal hemoglobin (Hb E) masking the Hb A2 on HPLC.

I. Background

Around 7% of the world's population comprises hemoglobinopathy gene carriers. Almost a total of 1317 Hb variants have been identified (HbVar database)[1], the four most common worldwide are Hb S, Hb E, Hb C, and Hb D, in the order of decreasing prevalence[2]. Hb E is the most prevalent variant in Southeast Asia (Thailand, Myanmar, Cambodia, Laos, Vietnam), where its prevalence is 30-60%[3,4,5,6]. The prevalence of Hb E in India is about 0-3.5% with an increased clustering in Kolkata (22%) and Assam (50-80%)[7].

Hemoglobin E variant results from a G→A substitution in codon 26 of the β globin gene, this produces an abnormal hemoglobin (glutamate is replaced by lysine) and activates a cryptic splice site at codon 25-27 of the β-globin gene, resulting consequently in abnormal processing for messenger RNA (mRNA). The level of normally spliced mRNA become reduced and because a new stop codon is generated, the abnormally spliced mRNA become nonfunctional [7,8]. Fortunately, only a minor activation of the alternative splicing pathway the mutation is associated with this mutation. Hence there is only a moderate reduction of the normally spliced β^E globin mRNA[72].

Hb E trait and Hb EE disease are mild disorders. Although Hb E alone does not cause any significant clinical problems, its interactions with various forms of α and β thalassemia produce a very wide range of clinical syndromes of varying severity[8,9].

Hb E has several compound heterozygotes with common and uncommon β-globin or α-globin gene mutations, the most serious Hb E syndrome is Hb Eβ^0-thalassemia. Different phenotypes could be noticed with the compound heterozygote state of Hb Eβ-thalassemia ranging from a complete lack of symptoms to transfusion dependency [7, 8, 3, 10].

Experiments were carried out in vitro at temperatures ranging from 38 to 41°C showed that there was mild instability of Hb E but there is no evidence that this is the case in vivo[15 9]. It is noticeable that, E allele causes mild thalassemia, while $\beta^E\beta^0$ thalassemia shows a severe phenotype, this marked paradox in phenotype could not be explained up till now. It is reported that Hb E is sensitive to oxidative stress {HbVar database}. Does this or other properties of Hb E can contribute to the severity of the disease? This question is still waiting for an answer[11].

The aim of this report is to present a case of Hb EE discovered accidentally during a routine work trying to cast shadow on some parameters.

II. Case Report

A Consent has been taken from a 26-year-old male, from Kolkata, India, came to Najran University Hospital, Saudi Arabia for routine investigation. He did not complain from anemia or receive treatment. He gave a history of hemolytic anemia because of infection with malaria and only one blood transfusion. On examination, there were no significant clinical findings such as organomegaly, icterus, or thalassemic bone changes.

CBC were carried out using Sysmex XS 500i (Sysmex, https://www.sysmex.com/). The results showed Hb of 13 g/dL, red blood cell (RBC) count of 6.8 x 10^{12}/L, mean corpuscular volume (MCV) of 55.6 fl, mean corpuscular hemoglobin (MCH) of 19.6 pg, MCHC concentration of 36 g/dL, and RBC distribution width (RDW-CV) of 20.7%. Peripheral blood smear

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showed frequent target cells, and spherocytes as shown in Fig.(1). Serum biochemical analysis were carried out using COBAS C311 (Roche, https://www.roche.com/). Results were normal for liver and kidney functions except for mild increase in bilirubin (1.39 mg/dL, mostly indirect of 0.98 mg/dL). Lipid profile was normal except for low high density lipoprotein cholesterol (HDL- C) of 20.6 mg/dL...Iron, UIBC and ferritin were found to be 73.3 ug/dL, 250 ug/dL and 149.6 ug/L respectively. Glucose was within normal ranges. Vitamin B_{12}, C-peptide, estradiol (E_2), follicle stimulating hormone (FSH), free triiodothyronine (FT_3), free thyroxine (FT_4), luteinizing hormone (LH), prolactin, parathyroid hormone (PTH), testosterone, thyroid stimulating hormone (TSH) and vitamin D_3 (25-OH) were done. C-peptide, E_2 and TSH results were slightly above the normal range. Vit D was slightly insufficient. Some parameters were indicated in table (1). Hb A1c did not give results on D-10 HPLC that is why we thought of Hb variant. Hemoglobin (Hb) separation by high performance liquid chromatography (HPLC) using the D-10 instrument (Bio-Rad Laboratories Hercules, California, USA) as in Fig. (2). Nearly all the Hb were abnormal and it was eluted at the Hb A2 window with retention time (rt) of 3.17 minutes. When repeated on Variant II HPLC system ((Bio-Rad) with use of the Variant II Thalassemia Short Program, it showed 86.1 % abnormal Hb with rt of 3.8 min along with 2.28 % adult Hb (Hb A) and Hb F around 3% of total Hb.

Table 1: Some hematological parameters:

Investigation	Values	Investigation	Values
Hb	13 g/dl	WBC	$11x10^9$/L
RBC	$6.8x10^{12}$/L	Eosinophilia	1.9×10^9/L
MCV	55.6 Fl	HDL-C	20.6 mg/dl
MCH	19.6 pg	C-Peptide	6.97 ng/ml
MCHC	36.3 g/dl	E2	46.88 pg/ml
Total bilirubin	1.39 mg/dl	TSH	6.8 μIU/ml
Indirect bilirubin	0.98 mg/dl	Vit-D (25-OH)	27 ng/ml
HDL	20.6 mg/dl		
UIBC	250 μg/dl		
Ferritin	149 μg/dl		
Iron	73.3 μg/dl		

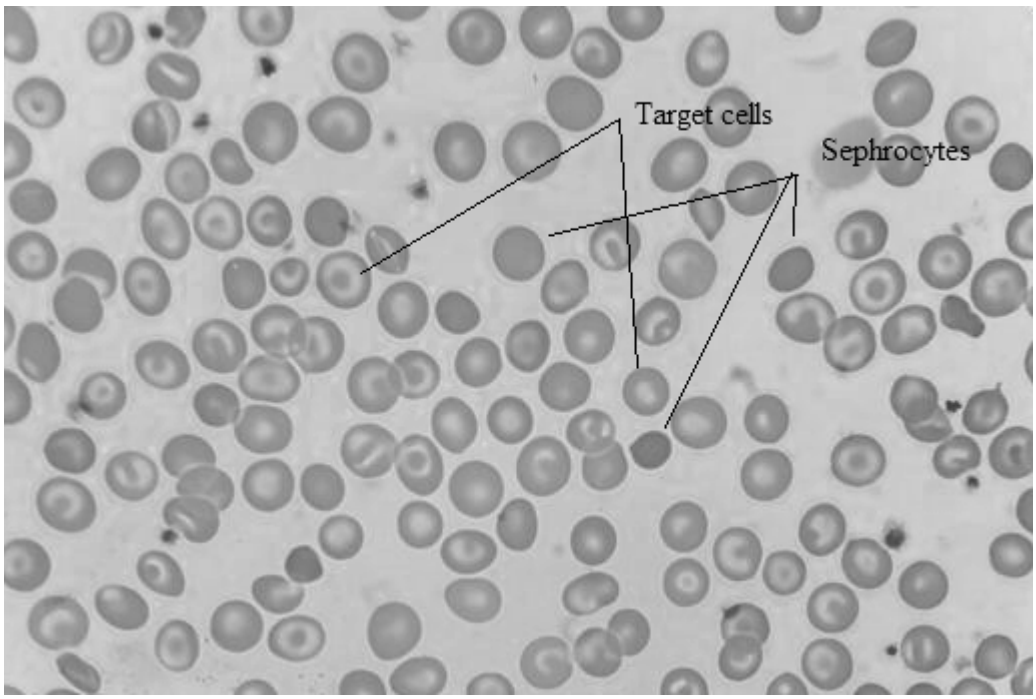


Fig. 1: Peripheral blood smear showing spherocytosis and Target cells.

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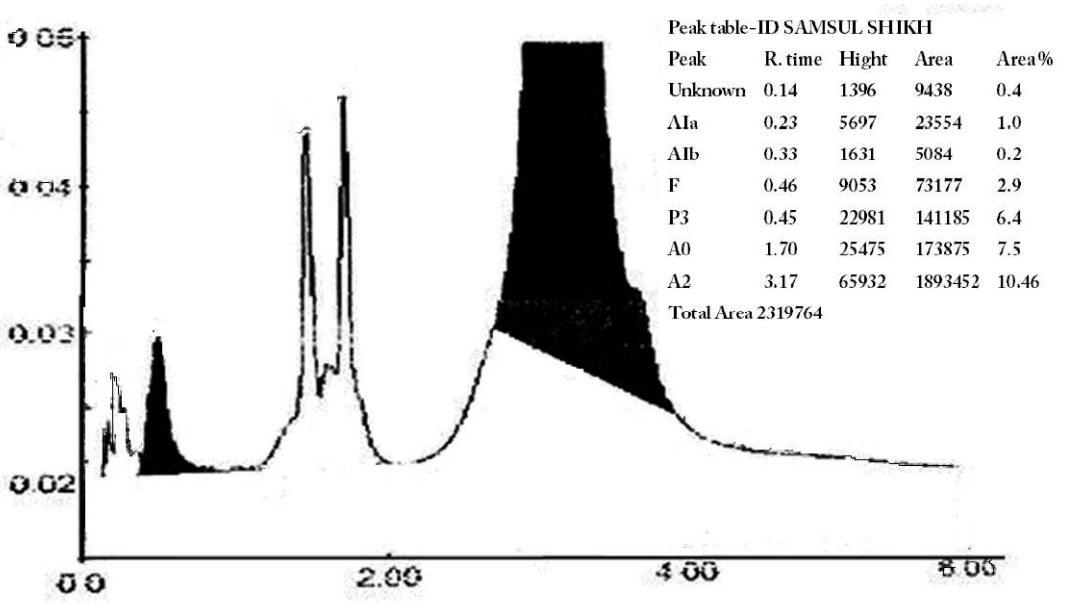


Fig. 2: HPLC separation of Hemoglobin. a) D-10

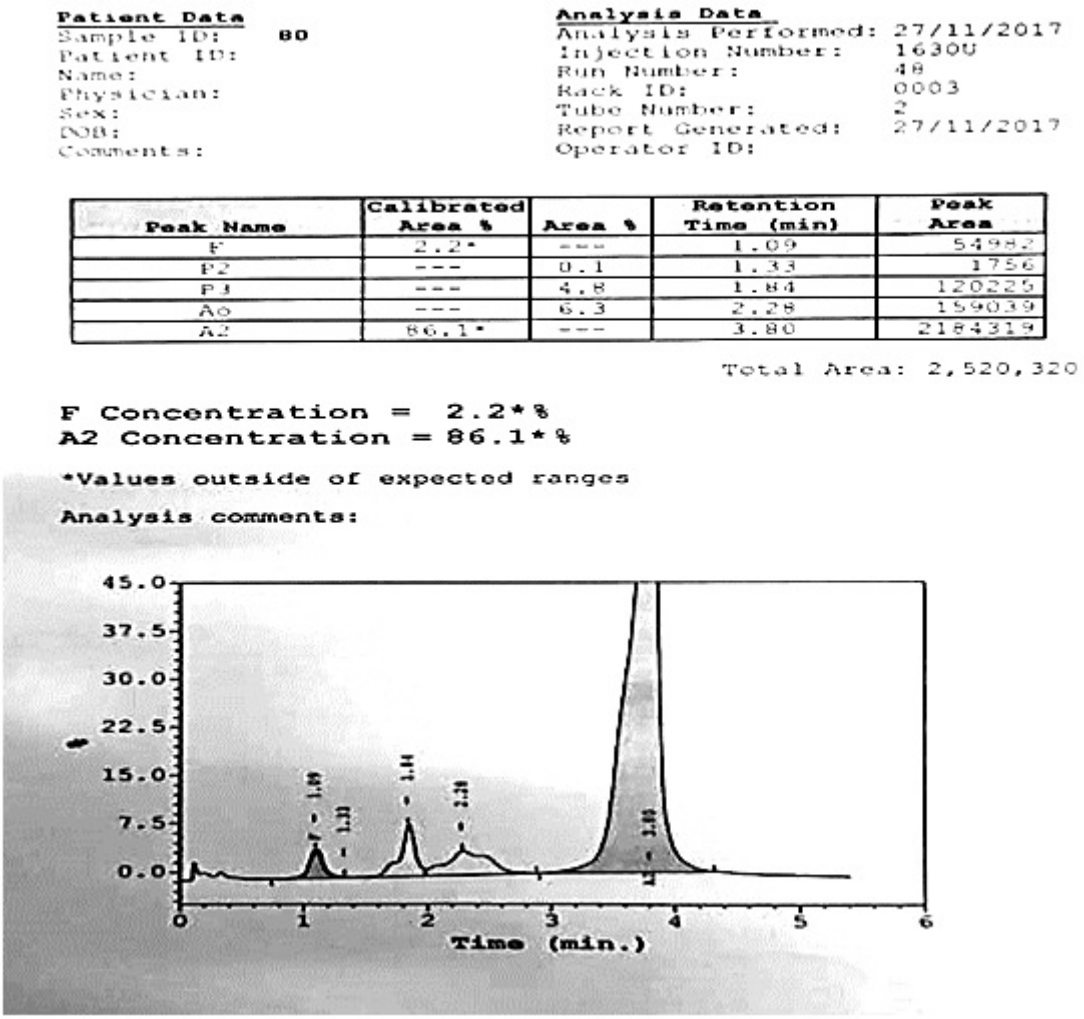


Fig. 3: HPLC separation of Hemoglobin. b) Variant II

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Stool examination was negative for parasites. Helicobacter pylori Antigen is stool and Abs in serum were negative by One Step H. pylori test device (ABON Biopharm, China). Malaria Ag in blood was negative by malaria P/F/Pan rapid test device from ABON, China. Clinical examination showed no abnormality.

III. Discussion

The majority of hemoglobinopathy present in the western and eastern provinces of Saudi Arabia. Abuzenadah et al.[7,3] , reported a great heterogeneity at the molecular level in the western province and attributed this to the large population of immigrants there. Hb E was one of the seven common β-thalassemia alleles reported.

Haemoglobinopathy is not common in Najran city. Prevalence reported by Memish et al., [12] of 14.7 % mostly sickle mutations of 14.1 % [8].

Considering his history, clinical findings and laboratory findings, the diagnosis in this case was homozygous Hb EE disease. The patient showed very mild, clinically asymptomatic, hemolytic microcytic hypochromic anemia with many target cells on peripheral blood smear characteristic of Hb EE disease which consistent with the classical presentation of the disease[9]. The presence of mild increase in Hb F indicates the mildness of the pathophysiology of the disease. The presence of a minute quantity of Hb A on HPLC was explained by post-translational modification of Hb E[13].

The patient gave a history of high fever due to malaria infection, with a hemolytic attack and he received a blood transfusion which could match the published of the instability of Hb E in high fever[14]. We noticed the presence of many spherocytes in the peripheral blood smear with an increase of MCHC. Similar findings occur in Hb C due an increase in the activity of K: Cl^- cotransport that induces the loss of K^+ and subsequently of intracellular water[15]. The patient has low HDL-C which could not be explained. Also the slightly increased hormones of E2 and TSH, the slightly increased C-peptide could not be explained and recommended for further investigation.

IV. Conclusion

Thus we report a case of abnormal hemoglobin (Hb E) masking the Hb A2 on HPLC. Knowledge of such a condition would help in prevention of misdiagnosis. Also we focused on some abnormal findings and recommended them for further research.

Acknowledgement

The team of this case report acknowledge Mr./Muhammad Shoaib Aslam, Medical laboratory technologist Najran University Hospital Ksa, for his cooperation and helps during different stages of this work.

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Global Journal of Medical Research: C
Microbiology and Pathology
Volume 19 Issue 2 Version 1.0 Year 2019
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Ocular Surface Squamous Neoplasia with Subepithelial Hemangioma: A Rare Case Report

By Indu Yadav, Sufian Zaheer & Rashmi Arora
Varhman Mahavir Medical College and Safdarjung Hospital

Abstract- OSSN represents the spectrum of disorder ranging from dysplastic changes to squamous cell carcinoma involving surface of an eye.[1] Conjunctival hemangioma is proliferation of blood vessels within the substantia propria. Ocular surface squamous neoplasia (OSSN) is a disease of the elderly [2] in western countries. However in African and certain part of asia, OSSN afflict youger patient and tend to be more clinically aggressive.[1],[3] We report a rare case of a OSSN with hemangioma in a young 33 year old male presented with fornix nodule in left eye. Diagnosis of hemangioma was made based on clinical suspicion. Definitive diagnosis needs histopathological evaluation.

Keywords: conjunctiva, ocular surface squamous neoplasia (OSSN), hemangioma.

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Ocular Surface Squamous Neoplasia with Subepithelial Hemangioma: A Rare Case Report

Indu Yadav [α], Sufian Zaheer [σ] & Rashmi Arora [ρ]

Abstract- OSSN represents the spectrum of disorder ranging from dysplastic changes to squamous cell carcinoma involving surface of an eye.[1] Conjunctival hemangioma is proliferation of blood vessels within the substantia propria. Ocular surface squamous neoplasia (OSSN) is a disease of the elderly [2] in western countries. However in African and certain part of asia, OSSN afflict youger patient and tend to be more clinically aggressive.[1],[3] We report a rare case of a OSSN with hemangioma in a young 33 year old male presented with fornix nodule in left eye. Diagnosis of hemangioma was made based on clinical suspicion. Definitive diagnosis needs histopathological evaluation.

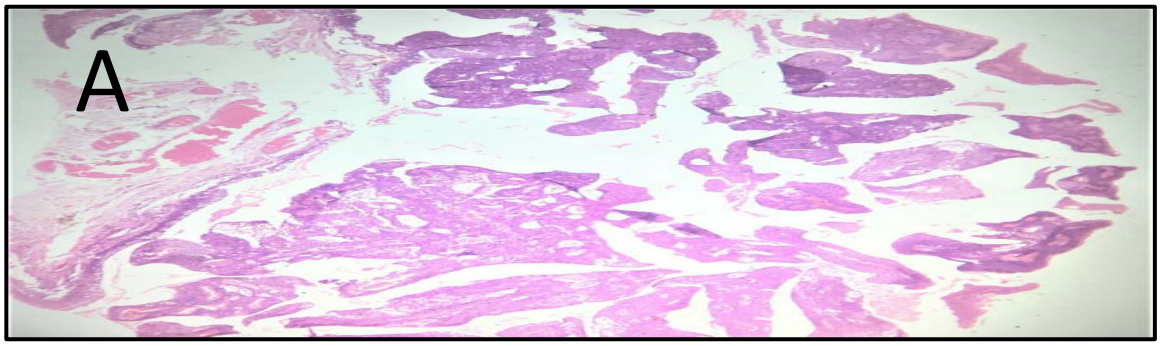
Keywords: conjunctiva, ocular surface squamous neoplasia (OSSN), hemangioma.

I. Introduction

Ocular surface squamous neoplasia (OSSN) is a wide spectrum of disease ranging from mild dysplasia to carcinoma in situ to invasive squamous cell carcinoma of the ocular surface. Most common site is limbus where most actrive mitotic cell reside.[4] OSSN is more common in equatorial countries where exposure to sunlight is more common. Risk factors for OSSN include male gender, ultraviolet light exposure, human papilloma virus (HPV) infection, human immune deficiency virus (HIV) infection.[4],[5],[6],[7] Clinically, the diagnosis is difficult due to variable presentation suspected by the appearance of epithelial changes of the of the ocular surface. OSSN may dissimulate chronic conjunctivitis, corneal ulcer, pterygium, necrotizing scleritis.[8] Slit-lamp examination shows gelatinous, papilliform or nodular lesions. Nodular is being the most common amongst it.[9] Histopathological evaluation is important for the definitive diagnosis. Immuno histochemically detectable p53 protein, bcl-2 protein, MIB-1 are being used as markers of proliferative potency having a possible prognostic value.[10] Capillary hemangioma is common in pediatric and adult age group and presents in early life.[11] We report a case of OSSN with hemangioma in a 33-year-old male who has been clinically diagnosed with hemangioma and subsequently been treated for it.

II. Case Report

A 33-year-old male presented with complaints of redness associated with itching in left eye for the past 6 month which was intermittent, recurrent and not associated with any painor discharge, eye surgery or trauma. He was a shopkeeper by profession. There was a history of multiple treatment regimens, including artificial tears, topical nonsteroidal anti-inflammatory drugs. He had no systemic illness and there was no lymphadenopathy. On examination, his best-corrected visual acuity was 20/20 both eye. On slit lamp examination of the left eye,a sessile papillary vascular mass in fornix was seen. Engorged conjunctival vessels were seen at the base of the lesion. The surface of the lesion was irregular. Blood investigations were normal. He underwent uneventful surgery in the left eye under local anesthesia .The excised lesion was sent for histopathological examination. Histopathology report showed a columnar lined epithelium of conjunctiva which shows dysplasia along with epithelomatous hyperplasia and papillomatosis. Dysplasia was from moderate to severe degree. Subepithelial tissue showed hemangioma so the diagnosis of ocular surface squamous neoplasia with severe dysplasia and subepithelial hemangioma was made. Postoperatively, the patient was given a course of topical antibiotic-steroid combination in tapering dose over 3 weeks, topical lubricants for 6 weeks.



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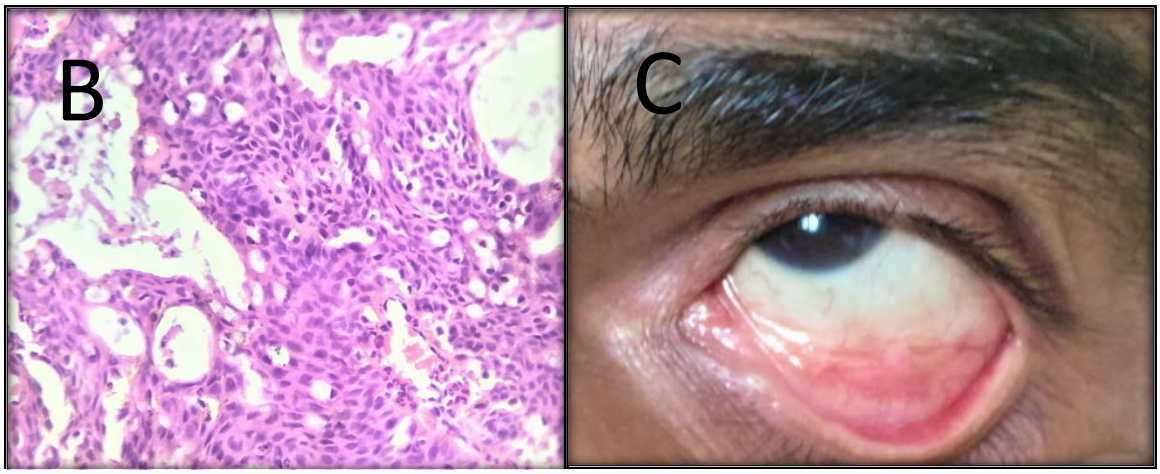


Fig. 1:

A. Photomicrograph from the left papillary mass in the fornix (4x magnification)
B. Photomicrograph showing dysplasia along with hemangioma (40x magnification)
C. Clinical photograph of left eye after removal of papillary mass.

III. Discussion

OSSN is a localized, slow growing lesion with low metastatic potential. OSSN has intraocular and orbital extension rate of 4%, regional and distant metastasis rate of 1.2%, and a mortality rate of 0.8%. Sites of metastasis are preauricular, cervical lymph nodes, the parotid gland, lungs, and bones. Regional lymph node involvement precedes the development of distant metastases.[12] What makes this case interesting is a rare presentation of subconjunctival hemangioma along with ocular surface squamous neoplasia The subconjunctival hemangiomas are rare vascular conjunctival lesions and presentation with OSSN is even rarer. Symptoms range from none to visual loss. Clinically its difficult to made diagnosis therefore definitive diagnosis is made by histopathological examination of the excision biopsyspecimen. Histopathological diagnosis is vital for both defining therapeutic options as well as for prognostication.[13] Nonsurgical options for small OSSN lesions include topical 5-FU and MMC drops. They eliminate the need to worry about the excised margins.[14] Surgical excision with "wide margin, no touch" technique is currently the best established form of treatment. Nevertheless, recurrences of these lesions are common after surgical excision, depending on the involvement of the surgical margins. Recurrence rates following excision of OSSN alone range from 15 to 52%, with an average of 30%. Recurrence rate is 5% when the surgical margins are free and 53% when the surgical margins are involved. [15]

In the management of OSSN, excision biopsy, though considered the gold standard.[4] Simple surgical excision is an option in small tumors, but the recurrence rates can be as high as 33% even in tumors excised with clear margins With adjuvant cryotherapy, the recurrence goes down to 12% in tumors excised with clear margins.[16] Surgical excision with adjuvant chemotherapy is another described technique with antimetabolites being given either intraoperatively or as drops postoperatively.[17] In our case, we used a combination of both intraoperative and postoperative MMC.

IV. Conclusion

Slow growth of lesions of OSSN and the ever present malignant potential makes regular follow-up of these patients for the remainder of their life mandatory.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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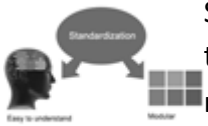


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6. Proper permissions must be acquired for the use of any copyrighted material.
7. Manuscript submitted *must not have been submitted or published elsewhere* and all authors must be aware of the submission.

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It is required for authors to declare all financial, institutional, and personal relationships with other individuals and organizations that could influence (bias) their research.

Policy on Plagiarism

Plagiarism is not acceptable in Global Journals submissions at all.

Plagiarized content will not be considered for publication. We reserve the right to inform authors' institutions about plagiarism detected either before or after publication. If plagiarism is identified, we will follow COPE guidelines:

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- Words (language)
- Ideas
- Findings
- Writings
- Diagrams
- Graphs
- Illustrations
- Lectures



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- Printed material
- Graphic representations
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- Electronic material
- Any other original work

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1. Substantial contributions to the conception and acquisition of data, analysis, and interpretation of findings.
2. Drafting the paper and revising it critically regarding important academic content.
3. Final approval of the version of the paper to be published.

Changes in Authorship

The corresponding author should mention the name and complete details of all co-authors during submission and in manuscript. We support addition, rearrangement, manipulation, and deletions in authors list till the early view publication of the journal. We expect that corresponding author will notify all co-authors of submission. We follow COPE guidelines for changes in authorship.

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Unless specified in the notification, the Editorial Board's decision on publication of the paper is final and cannot be appealed before making the major change in the manuscript.

Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

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Preparing your Manuscript

Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.

Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11'", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.



Format Structure

It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.



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6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

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To make a paper clear: Adhere to recommended page limits.



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Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.



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Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

The Administration Rules

Administration Rules to Be Strictly Followed before Submitting Your Research Paper to Global Journals Inc.

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Segment draft and final research paper: You have to strictly follow the template of a research paper, failing which your paper may get rejected. You are expected to write each part of the paper wholly on your own. The peer reviewers need to identify your own perspective of the concepts in your own terms. Please do not extract straight from any other source, and do not rephrase someone else's analysis. Do not allow anyone else to proofread your manuscript.

Written material: You may discuss this with your guides and key sources. Do not copy anyone else's paper, even if this is only imitation, otherwise it will be rejected on the grounds of plagiarism, which is illegal. Various methods to avoid plagiarism are strictly applied by us to every paper, and, if found guilty, you may be blacklisted, which could affect your career adversely. To guard yourself and others from possible illegal use, please do not permit anyone to use or even read your paper and file.

Criterion for Grading a Research Paper (Compilation) by Global Journals

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals.

Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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ISSN 9755896

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